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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,610	12/10/1999	ELIZABETH G. NABEL	8642/88	9076

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	28

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/458,610	NABEL ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/3/04* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/4/03 has been entered. As requested, the accompanying declaration of Elizabeth Nabel under 37 CFR 1.132 and the amendment have also been entered. Claims 106-142 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action, paper no. 11.

Claim Rejections - 35 USC § 112

The rejection of claims 106-142 under 35 U.S.C. 112, first paragraph, for lack of enablement is **maintained** over claims 109-142 and **withdrawn** over claims 106-108. Applicant's amendments to the claims, arguments, and the declaration by Dr. Nabel under 37 CFR 1.132

have been fully considered but have not been found persuasive in overcoming the following grounds of rejection of claims 109-142 for reasons of record discussed in detail below.

Please note that the rejection of claims 106-108 has been withdrawn in view of applicant's declaratory data which provides a second example of protein production *in vivo* following site specific installation of vascular smooth muscle cells transduced with an adenovirus encoding p27, the first example being the applicant's working example demonstrating marker gene expression presented in the instant specification. While p27 is not disclosed in the specification or available in the prior art, p27 was first reported in 1994, the declaratory data is effective in demonstrating that transduced smooth muscle cells can in fact produce a protein *in vivo.* While the applicant argues that this data provides proof that the use of the instant methods for treating diseases is established for the entirety of the claimed subject matter, the office disagrees, see below for a detailed discussion of the applicant's declaratory data. Never-the-less, the examiner has located on page 31 of the specification an alternative use for expression of a protein *in vivo*. Page 31, lines 4-7 state that expression of a marker gene from transformed cells *in vivo* can be used to monitor cell migration. Based on this use for the methods of claims 106-108, the enablement rejection over these claims has been withdrawn.

The applicant's amendment to claim 115 to recite the instillation of "transformed" cells has overcome the previous grounds of rejection regarding the lack of enablement for the installation of untransformed cells. However, this amendment does not overcome the lack of

enablement provided by the specification for "treating a human patient" using transformed cells according to applicant's claimed methods, see discussion below.

As noted above, the applicant argues that the declaratory data using transduced smooth muscle cells which express p27 to inhibit neointimal hyperplasia following balloon angioplasty provides evidence that the use of the instant methods for treating diseases is established for the entirety of the claimed subject matter. The office, however, does not find that the declaratory data provides enablement commensurate in scope with the breadth of the instant claims as written. As a first issue, the specification does not disclose the p27 protein. Enablement under 35 U.S.C. 112, first paragraph, is assessed according to the state of the art as of the effective filing date of the specification. The instant application has an effective filing date of 3/31/89. However, the p27 protein was not identified and reported in the literature until 1994. As stated in *In re Glass*, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications or evidence which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. While the specification does in fact disclose a number of proteins that could be used in applicant's methods, as pointed out by the applicants on page 9 of the instant response, no data regarding these putative therapeutic proteins has been presented in the specification or made of record. As noted in previous office actions, the specification's working examples demonstrate the transfection of endothelial cells with a vector encoding lac-Z, and the installation of these cells by

balloon catheter to blood vessels *in vivo*. The specification reports that the endothelial cells expressed detectable levels of β-galactosidase following transplantation. The specification also states that expression could be detected for approximately six weeks. However, the specification does not correlate the level of β-galactosidase with any therapeutic effect on any disease symptom or teach that the expression of similar levels of any other protein, such as FGF or tPA, for similar periods of time would result in any effect on any cardiovascular condition such as atherosclerosis, restenosis, or heart disease.

Furthermore, assuming *arguendo* that the applicant's data using p27 were probative in determining the enablement of the instant application of methods of treating humans, the single example provided which demonstrates that the expression of p27 from vascular smooth muscle cells delivered by catheter to the femoral artery can inhibit catheter-induced neointimal hyperplasia does not provide a scope of enablement that correlates with the breadth of applicant's claimed methods. The methods claims read on the treatment of any type of disease in a patient. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The diseases recited in the specification include diabetes, liver disease, hypercholesterolemia, malignancy, HIV, cardiomyopathy and peripheral vascular disease. These diseases have substantially different etiology than injury induced neointimal hyperplasia, and are likely caused by substantially different factors, both genetic and environmental. As noted in the previous office actions, while the specification lists several candidate genes products that

might be useful to treat one of the listed diseases, the specification fails to provide guidance as to the level of gene expression of any of these putative therapeutic genes that correlates with an effect on any of the above listed conditions. Further, the references cited in the previous office actions, Verma et al., Ledley et al., and Orkin et al., teach the unpredictability of achieving therapeutic levels of expression of a transgene in vivo by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector, and the unpredictability of treating disease using gene therapy. Thus, contrary to applicants assertion, the skilled artisan would not have predicted either at the time of the effective filing date of the instant application, or today, that the expression of any level of a putative therapeutic protein from transduced endothelial, smooth muscle or parenchymal cells would result in a therapeutic effect on the disease to be treated. Therefore, in view of the substantial differences between diseases such as diabetes, liver disease, HIV, and injury-induced neointimal hyperplasia, the art-recognized unpredictability in achieving therapeutic levels of gene expression *in vivo* capable of treating a disease, and the breadth of the claims, the skilled artisan would not accept the declaratory data as providing enablement which reasonably correlates with the breath of the claims as written.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 106-109, 114-118, 121-131, 136, 142 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of U.S. Patent No. 6,203,991 (3/20/01), hereafter referred to as the '991 patent. Although the conflicting claims are not identical, they are not patentable distinct from each other for the following reason. The patented claims are both broader and narrower than the instant claims. Claims 8-14 of the '991 patent represent a species of the instant invention in that the '991 claims are directed to methods of inhibiting vascular smooth muscle cell proliferation by locally administering a nucleic acid encoding the heme oxygenerase 1 gene (claim 8), most specifically by administering a device

coated with cells, endothelial cells (claim 14), comprising the nucleic acid (claim 13). The '991 claims further recite the use of various types of devices, including stents, grafts, and catheters (claim 11) and in particular various kinds of catheters, injection catheters, balloon catheters, double balloon catheters etc. (claim 10). The instant claims are broader in that they recite methods of introducing a protein in mammal and methods of treating a human patient and are not limited to the inhibition of smooth muscle cell proliferation or to the heme oxygenerase 1 gene. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978). In other aspects of the invention, the '991 claims are broader than the instant claims. The instant claims recite wherein the cells originate or are syngeneic to the patient. While the '991 claims do not specifically include this limitation, the specification of the '991 patent clearly teaches ex-vivo gene therapy where cells from the patient are removed and transfected in vitro and then reseeded into the patient (the '991 patent, column 11, lines, 8-21, and column 14, lines 8-13). Therefore, the '911 claims clearly encompass the limitation in the instant claims relating to the use of cells originating from the patient. Thus, by teaching all the limitations of the instant claims as written, claims 8-14 render the instant claims obvious.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER